## 2087

## Downloaded by: University of Southern California. Copyrighted material.

## Studies towards the Synthesis of Coprinolone, $\Delta^6$ -Coprinolone, and Radulone A via an Anionic Electrocyclization Cascade

Andrew L. Lawrence, Victor Lee,\* Robert M. Adlington\*

Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK Fax +44(1865)275632; E-mail: robert.adlington@chem.ox.ac.uk; E-mail: victor.lee@chem.ox.ac.uk *Received 9 May 2008* 

Dedicated to Professor Sir Jack E. Baldwin in celebration of his 70th birthday

**Abstract:** Studies towards the synthesis of coprinolone,  $\Delta^6$ -coprinolone, and radulone A, resulting in the synthesis of an advanced intermediate with the tricyclic protoilludane carbon skeleton, are described.

**Key words:** electrocyclic reactions, protoilludane, sesquiterpenes, trienone, cascade reactions

Coprinolone (1),  $\Delta^6$ -coprinolone (2), and radulone A (3) are structurally intriguing oxygen-bridged protoilludane sesquiterpene ketols, isolated from *Basidiomycota* fungi (Figure 1).<sup>1,2</sup> Their compact tricyclic ether bridged carbon frameworks and large concentration of contiguous stereogenic centers, two of which are quaternary, make these novel sesquiterpenes attractive targets for total synthesis. Radulone A (3) has an interesting biological profile as a potent inhibitor of human and bovine platelet aggregation, as well as cytotoxic and antimicrobial activity.<sup>2</sup> Additionally, the protoilludanes are involved in the biosynthesis of many other sesquiterpenes,<sup>3</sup> and so a general approach to their synthesis could prove useful in future biomimetic approaches to related natural products.

With this in mind, an electrocyclization cascade route to the protoilludane skeleton was investigated. Results from our model studies were reported earlier, and are summarized below (Scheme 1).<sup>4</sup> With these promising results in hand, we envisaged that several natural sesquiterpenes oxygenated at C8, including 1-3, could be synthesized from one common intermediate 5 (Figure 1).

Efforts towards trienone **5** began with the Diels–Alder reaction between methyl methacrylate and butadiene to give cyclohexene **12**. This was followed by LiAlH<sub>4</sub> reduction and PMB protection to yield cyclohexene **13** (Scheme 2). The double bond in the PMB-protected alcohol **13** was then oxidatively cleaved to the diacid using Borhan's 'organometallic ozonolysis' procedure,<sup>5</sup> as standard ozonolysis gave low yields. The diacid was not isolated but esterified directly to the diester **14**, using the standard conditions of MeI and K<sub>2</sub>CO<sub>3</sub> in DMF. Pleasingly, Dieckmann cyclization of diester **14** gave exclusively the desired regioisomer **15** in excellent yield (Scheme 2).<sup>6</sup>

SYNLETT 2008, No. 14, pp 2087–2088 Advanced online publication: 15.07.2008 DOI: 10.1055/s-2008-1078569; Art ID: D15008ST © Georg Thieme Verlag Stuttgart · New York



Figure 1 Structures of selected protoilludane natural products 1–3, and proposed advanced intermediates 4 and 5



Scheme 1 Summary of previous model studies. *Reagents and conditions:* (a) DMSO, 100  $^{\circ}$ C, 2 h, 59%; (b) MeOH, 110  $^{\circ}$ C, 24 h, 33%; (c) MeOH, 110  $^{\circ}$ C, 3.5 h, 24%.

With cyclopentanone **15** readily available in multigram quantities it was hoped that the synthesis of trienone **5** would be a simple case of applying analogous transformations developed for model systems **6–8**.<sup>4</sup> However, the substituents on the cyclopentane ring in **15** proved to have a pronounced affect upon the reactivity of the molecule. Use of triflic anhydride to form vinyl triflate **16** proved very low yielding, thus Comins reagent [*N*-(2-pyridyl)triflimide] was employed which gave an excellent yield of 95% (Scheme 3).<sup>7</sup> Introduction of the isopropenyl group was achieved in our model systems using a Suzuki–Miyaura cross-coupling reaction.<sup>4</sup> Application of these conditions to **16** resulted in very poor yields; however, af-



Scheme 2 Reagents and conditions: (a) 180 °C, excess butadiene, hydroquinone (5 mol%), 92%; (b) LiAlH<sub>4</sub>, THF, 0 °C, 89%; (c) PMBCl, NaH, cat. *t*-Bu<sub>4</sub>NI, THF, reflux, 100%; (d) OsO<sub>4</sub>, Oxone, DMF, r.t.; (e) MeI,  $K_2CO_3$ , DMF, r.t., 74% over two steps; (f) KOt-Bu, THF, r.t., 99%.

ter screening many conditions, including various Stille reactions, it was found that a simple Negishi reaction provided diene-ester **17** in 82% yield (Scheme 3).<sup>8</sup> Reduction of ester **17** to aldehyde **18** was achieved via DIBAL-H reduction followed by  $MnO_2$  oxidation. Zinc-mediated crotylation<sup>9</sup> of **18** and final IBX oxidation<sup>10</sup> provided trienone **5** in 73% overall yield for the four steps, on a gram scale and with just one final chromatographic purification required (Scheme 3).



Scheme 3 *Reagents and conditions:* (a) Comins reagent, NaH, THF, r.t., 95%; (b) 2-bromopropene, *t*-BuLi, ZnCl<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, THF, -78 °C to r.t., 82%; (c) DIBAL-H, Et<sub>2</sub>O, -78 °C; (d) MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, r.t.; (e) Zn, crotyl bromide, aq NH<sub>4</sub>Cl–THF (1:2), 0 °C; (f) IBX, DMSO, r.t., 73% over four steps.

Studies on the model trienones **6–8** had shown that simple heating in polar solvents provided the tricyclic products **9–11** in moderate yields (Scheme 1).<sup>4</sup> Upon heating trienone **5** in DMSO at 150 °C, even for extended periods of time resulted in a yield of 16% of enone **20** (Table 1). It was therefore decided to explore the idea that formation

of the conjugated enolate of trienone **5** may possibly facilitate the  $8\pi$ - $6\pi$  electrocyclization cascade, in an analogous manner to the anionic oxy-Cope rearrangement.<sup>11</sup>

Use of DBU in benzene on model system **6** only led to double bond migration,<sup>4</sup> so it was decided to deprotonate trienone **5** irreversibly using a strong base, and preliminary results for the electrocyclization are promising (Table 1).

 Table 1
 Preliminary Results of the Electrocyclization of Trienone 5



Solvent	Base (equiv)	Temp (°C)	Time (h)	Yield (%) <sup>a</sup>
DMSO	none	150	80	16
DME	NaH (1.5)	85	20	22
DME	NaHMDS (1.5)	85	12	47

<sup>a</sup> Isolated yield; mixture of isomers.

Further work investigating the anionic electrocyclic ring closure of trienones, using our previous model systems **6**–**8**, and elaboration of enone **20** to form natural sesquiterpenes, for example **1**–**3**, is currently underway and will be reported in due course.

## **References and Notes**

- (1) (a) Starrat, A. N.; Ward, E. W. B.; Stothers, J. B. *Can. J. Chem.* **1989**, *67*, 417. (b) Starrat, A. N.; Ward, E. W. B.; Stothers, J. B. *J. Chem. Soc., Chem. Commun.* **1988**, *9*, 590.
- (2) Fabian, K.; Lorenzen, K.; Anke, T.; Johansson, M.; Sterner, O. Z. Naturforsch., C: Biosci. 1998, 53, 939.
- (3) Abraham, W. R. *Curr. Med. Chem.* **2001**, *8*, 583.
- (4) Lawrence, A. L.; Wegner, H. A.; Jacobsen, M. F.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron Lett.* 2006, 47, 8717.
- (5) Travis, B. R.; Narayan, R. S.; Borhan, B. J. Am. Chem. Soc. 2001, 124, 3824.
- (6) (a) Peelen, T. J.; Chi, Y.; English, E. P.; Gellman, S. H. Org. Lett. 2004, 6, 4411. (b) It should be noted that addition of the diester to the basic solution had to be slow (≥ 4 h) otherwise low yields of impure product were obtained.
- (7) (a) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* 1992, 42, 6299. (b) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. Org. Synth. 1997, 74, 77.
- (8) General procedure for Pd-catalyzed Negishi coupling taken from: Milne, J. E.; Buchwald, S. L. J. Am. Chem. Soc. 2004, 126, 13028.
- (9) Luche, J. L.; Petrier, C.; Einhorn, J. *Tetrahedron Lett.* 1985, 26, 1445.
- (10) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.
- (11) Snider, B. B.; Harvey, T. C. J. Org. Chem. 1994, 59, 504.